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Selected Papers
from the
BUREAU of
RADIOLOGICAL HEALTH
Seminar Program

The EFFECTS of IONIZING RADIATION on the DEVELOPING EMBRYO and FETUS

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FOREWORD

The Bureau of Radiological Health, formerly the National Center for Radiological Health, carries out a nationwide program designed to reduce the exposure of man to hazardous ionizing and nonionizing radiation.

Within the Bureau, the Office of Information disseminates information about the significant events occurring in the field of radiological health. In pursuit of this mission, the Office conducts a program of seminars and symposia. When a presentation is believed to be of especial interest, the speaker is invited to publish in this series entitled "Selected Papers from the Bureau of Radiological Health Seminar Program."

The Bureau also publishes the monthly **Radiological Health Data and Reports,** and special division technical reports. These publications are intended to provide a vehicle for conveying the results of radiological health studies to audiences which have specific interests.

The Selected Papers are distributed to State and local radiological health program personnel, Bureau technical staff, advisory committee members, university radiation safety officers, libraries and information services, industry, hospitals, schools, and other interested individuals. These reports are also included in the collection announced and made available by the Clearinghouse for Federal Scientific and Technical Information.

I encourage the readers of these reports to inform the Bureau of their opinions of these papers and of their value to the radiological health community.

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Dr. Rugh was born in Springfield, Ohio, but spent most of his youth in China (Shanghai). He graduated from New York's Yonkers High School as class valedictorian in 1922 and then pursued his academic life at Oberlin College where he was awarded his Bachelor's degree in 1926 and his Master of Arts degree in 1927.

In 1926, Dr. Rugh married Harriette Sheldon and, after teaching for a short while at Lawrence College in Appleton, Wisconsin, was awarded a graduate assistantship at Columbia University and, simultaneously, a full-time appointment as an Instructor in Biology at Hunter College in New York. Dr. Rugh received his Ph.D. degree from Columbia University in 1935.

In 1939, Dr. Rugh was offered, and accepted, a position of Assistant Professor of Biology at New York University to teach vertebrate embryology and to develop a new course in experimental embryology. Following ten years at New York University, during which he authored a laboratory manual on vertebrate embryology which is still widely used and a textbook on the Frog, he accepted an appointment at the College of Physicians and Surgeons (Columbia University) to direct an AEC supported research program in radiobiology. Since 1949, while in a teaching position at Columbia University, Dr. Rugh has published 156 papers in scientific journals around the world. Most of these papers have dealt with the biological effects of radiation exposure. Prior to 1949, while at N.Y.U., he had authored some 57 technical papers which have been published in a variety of journals.

Dr. Rugh's writing has also included authorship of a number of books. The one he has found to be most exciting is scheduled for release in the fall of 1970 and is entitled *From Conception to Birth, The Drama of Life's Beginnings*. This has been written to enable a pregnant woman to gain an appreciation of exactly how her child is developing. The publishers are highly optimistic about its sales appeal. It will have 35 color plates of human fetuses.

Dr. Rugh, as one might expect, has been the recipient of many honors for his scientific endeavors. He is listed in Who's Who in America, Who's Who in the East, American Men of Science, and Leaders in American Science. He is a member of 14 scientific societies, mostly in the fields of radiation or embryology.

The Rugh's have two children of which they are very proud and are looking forward to retirement in 1971. Dr. Rugh feels that after his retirement he will continue to teach and write.

THE EFFECTS OF IONIZING RADIATION ON THE DEVELOPING EMBRYO AND FETUS

ROBERTS RUGH, Ph.D.

Ionizing radiations, from whatever source, have an immediate physical effect in and on any biological system. This physical effect results in chemical adjustments which, in turn, bring about biological sequelae which are classified under the broad term **biological effects of ionizing radiations.** There is no question as to the immediacy of the physical effects of ionizing radiations and their potency when one realizes that the ionization of only one molecule in 10 million is lethal for any mammalian system. Both x- and gamma rays generate high speed charged particles, usually electrons, which move so fast that they approach the speed of light. Such fast particles, by means of their electric fields, act on atoms by tearing away some of the component electrons. As a result, these atoms are ionized and this then is the primary physical effect of such radiations. Chemical changes are usually slower and, in the highly complex chemistry of any biological system, are often irreversible. The consequences tend to be inevitable and detectable, but generally require some lapse of time. It may well be that it is the chemical alterations which bring about the ultimate biological effects, rather than the initiating physical ionizations, but their evaluation is often difficult because they may take an indefinite period of time to become apparent. For example, radiation-induced cancer of the skin has been known to have a latent period of 35 years or more in some susceptible individuals, even though the original exposure to radiations may have been almost instantaneous. In discussing the biological effects of ionizing radiations it is necessary to understand that the initiating cause, an ionization, may be point specific and instantaneous; that the time variations in the biological response give evidence of being related to the innate susceptibility of the reacting tissue, organ, or host and, therefore, may range from hours to many years, or even may never occur. Finally, there is evidence to suggest that the different qualities (electron densities) of ionizations from alpha, beta, gamma or x-ray sources would elicit essentially the same physical responses in any biological system if the ionizations occur at the same molecular level.

The terms **repair** and **recovery** are appearing more and more frequently in the radiobiological literature and, while they are often applied to the biological effects of ionizing radiations, they have their origin in medical practice. To repair a broken bone or to recover from pneumonia are precise terms to describe what happens, but when the same words are used to imply a complete reversion of a biological system to its pre-radiation state, it is taking semantic license which cannot be justified at the moment. When ionizing radiations penetrate a biological system and molecules are ionized, there is, as yet, no clinical support for the idea that such changes are temporary or that the biological responses are reversible so that the pre-radiation status is reestablished. Even when chromosomes are broken by radiations and, are later rejoined, only statistically valid genetic experiments which prove that the linear order of the genes had not been changed would allow us to state that there had been no permanent effects caused by the ionizing

[1]This paper was presented as part of the National Center for Radiological Health's (now the Bureau of Radiological Health) Seminar Program on February 14, 1969 in Rockville, Maryland.

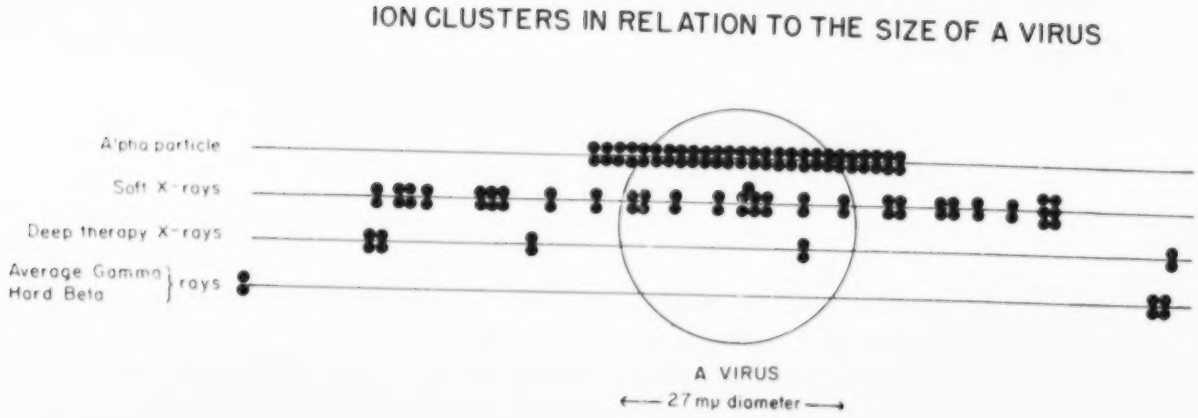


Fig. 1 The various qualities of ionizing radiations have essentially the same effect on biological systems. But, it is the ionization in tissue that counts and this diagram illustrates one of the differences between the several types of irradiations used. The black spots indicate ionizations, which are the biologically effective physical entity. Note that the circle (a hypothetical virus) is ionized by many units from the alpha source, less from the soft and deep therapy x-rays, and still less from the gammas or hard betas. It is possible to miss ionizing a molecule or a virus by a beta exposure, but the concentrations from an alpha source, if an ionization hits the virus will be many hits. This is described as linear ion density, which shows how one source could have a different effect on a biological system than another, simply by a different concentration of ionizations.

radiations. It is difficult to believe that any physical trauma as drastic or violent (at the molecular level) as radiations would bring about reversible type biological changes. The fact that x-irradiated skin may lose its erythema and revert to normal color, leaving no observable radiation scar, cannot mean complete recovery when, after 35 years, a squamous cell carcinoma develops in that skin area as an obvious result of the single exposure to ionizing radiations. Thus, if the terms **repair** or **recovery** are used to describe biological reactions to ionizing radiations, they must be specifically delimited and so defined that the normal clinical usage is not implied. It is my contention that any biological change caused by ionizing radiations, regardless of its effect on the system, is irrevocable and irreparable, in the sense that there is never a return to the exact pre-irradiation status. This would most obviously apply at the sub-microscopic level. Recognition of these facts must force us to respect the potency of ionizing radiations as never before.

Ionizing radiations are known to fragment chromosomes, to cause them to assume bizarre shapes and to become sticky so that they adhere to one another. It is inconceivable that parts of a fragmented chromosome will act like a magnet and rejoin its dismembered part in exactly its original form. Rather, the element of chance suggests that the stickiness which affects all chromosomes that have been x-irradiated will cause those in near proximity to join and, to join in a haphazard manner. This results in new karyotype combinations. Even genetic studies might demonstrate an undisturbed genotype, but the linear order of the genes may still have been drastically altered. Thus, until there is adequate evidence to the contrary, it must be assumed that chromosomes altered by ionizing radiations do not tend to return to their prior arrangement. Strictly speaking, radiation effects in any biological system are most likely permanent, particular at the ultra microscopic level.

To researchers in radiation biology it is readily evident that there exists a differential, and often unpredictable, radiosensitivity. This is true not only among phyla, species, heterozygous individuals, but also among organs, tissues, and cells. For this reason, radiobiological conclusions cannot be extrapolated from one strain of animals to another. The search for a common denominator of biological reactions has been futile. The single celled

organisms (protozoa, algae, viruses, bacteria) seem to be highly resistant; the cockroach can tolerate 60,000 R, but the chicken only 1,400 R, man about 400 R and the guinea pig about 225 R. Thus there is no correlation of radiosensitivity with the position in any evolutionary scale. It has been suggested, since tissues of a mammal can be arranged in order of degree of hydration and such a scale does bear some relation to increased radiosensitivity with hydration, that possibly the chemical production of hydrogen peroxide in tissues might be the poison that causes radiation death. Certainly epithelium, spleen, and blood are tissues of high hydration and high radiosensitivity while bone, cartilage, and nerves are low in water and low in radiosensitivity. But, then, the Protozoa, as a class, are highly aqueous and yet very radioresistant while the human, with about 60% hydration, is relatively radiosensitive. The ever expanding volume of research data will allow us to categorize various animals, organs, tissues, and even cells, as more or less radiosensitive. However this information is empirical and can never be extrapolated or anticipated.

The fact that different animals have different radiosensitivities is borne out by the LD/50/30 studies (lethal dose to 50% in 30 days following whole body exposure). The reactions of animals to whole body exposure to ionizing radiations are never **all-or none**, never clear cut and uniform. In any normal population a wide range of reactions found to the identical radiation exposure. The range of reaction extends from those that die soon to some that do not die before their normal life expectancy has been reached. Animals which appear to be identical with respect to species, age, weight, sex, and general health will often show three peaks of lethality following whole body exposure to x-rays at the LD/50/30 level. (a) None will die within the first 3½ days, but may be expected to die soon thereafter from hemorrhages. (b) Some will die after about two weeks due to destruction and malfunction of the gastrointestinal tract. (c) Still others will die later from secondary infections, probably resulting from the radiation induced leukopenia. And yet 50% will live well beyond the 30 day test period, some as long as their normal life expectancy.

The LD/50/30 for the human is 400 R whole body penetrating x- or gamma radiation and the LD/100/30 is 600 R. The LD/100/30 means that all would die at this level of exposure within 30 days. The fact that after 400 R half of the exposed population survives suggests that there must be individual factors which contribute to differences in radioresistance. It has been established that female hormones help and, in general, females of any species tend to tolerate radiation exposures better than males with otherwise equal biological factors. Weight, age, activity, and other variables are contributory, but the least investigated and probably the most significant are the hereditary variations. Inherent radioresistance is a fact, as is inherent radiosensitivity, and any species of animals which otherwise appear to be identical will show a wide range of sensitivity. When species are crossed, the resultant hybrids are more radioresistant than either of their progenitors, exemplifying heterosis. Thus, in any heterozygous population, which applies to most human populations, one would expect greater radioresistance than in any purebred or inbred line and would expect to find also a wide range of differences in radiosensitivity. Like any susceptibilities, such as cancer, radiosensitivity seems to be altered by heredity . . . within certain limits.

Experimental evidence points out that while the physical entity (radiations) may be uniform and the chemical changes that ensue might be rather delimited, the end result in terms of biological response will depend to some degree upon the genetic or inherited potential of the reacting system which, in a heterozygous population, would be quite wide.

Why, then, are embryos and fetuses so particularly radiosensitive; why do they exhibit such a wide range of congenital anomalies; can radiation induced congenital anomalies be prevented; and why is radiation diagnosis and therapy of the human female pelvis such a criticial procedure?

First, let's answer these questions and then give specific examples.

TABLE 1 The LD/50/30 Days For Various Animals

Animal	Type Radiation	Dose Range
Guinea Pig	x-rays	175 R-409 R
Swine	x-rays	275 R
Dog	x-rays	300 R-430 R
	Sr-89	1.0 uc/gm.
Goat	x-rays	350 R
	Sr-89	1.0-1.5 uc/gm.
Man (interpolated)	x-rays	400 R
Monkey	x-rays	500 R
Mouse	x-rays	400 R-650 R
	fast neutrons	54 n-200 n
	alphas (radon)	0.014 mc/gm.
	betas	250 uc
Rat	x-rays	590 R-970 R
	betas (P^{32})	4.5 uc/gm.
Goldfish	x-rays	670 R
Frog	x-rays	700 R
Hamster	x-rays	725 R
Rabbit	x-rays	750 R-825 R
	fast neutrons	125 n
Chicken	x-rays	1,000 R
Turtle	x-rays	1,500 R
Triton	x-rays	3,000 R
B. Coli	x-rays	5,600 R
Snail	x-rays	8,000 R to 20,000 R
Yeast	x-rays	30,000 R
Amoeba	x-rays	100,000 R
B. Mesentericus	x-rays	150,000 R
Colpidium Colpoda	x-rays	330,000 R
Paramecium Caudatum	x-rays	350,000 R

Mitosis, or cell division, shows cyclical changes in radiosensitivity, with the maximum sensitivity appearing to occur at metaphase and anaphase. The so-called resting cell or intermitotic phase appears to be the least sensitive stage. This, however, would be a misleading assessment because the cells which had been exposed in the intermitotic phase will tend to respond at the time they begin their subsequent mitosis, often going to pieces at the usually expected critical phase. In any case, cells which show a high mitotic index **do** have a high level of radiosensitivity so that one would expect, in somatic tissues, a greater response to be observed in epithelium than in cartilage or nerve. The entire embryo or fetus has the highest mitotic index because some 800 billion cells must be derived from a single fertilized ovum, all by mitosis. So, from the beginning, and throughout the development of the embryo and the fetus, the cells, because of intense mitotic activity, should be, and are, highly radiosensitive.

Mitosis involves chromosome formation and it is simple to demonstrate that formed chromosomes are sensitive targets for ionizing radiations. Aneuploidy caused by radiations in embryonic or fetal cells is frequently seen. The exact relation between aneuploidy and congenital anomalies has not been established, but is likely quite close. In any case, when one exposes an embryo or fetus to any ionizing radiations, there are always many formed chromosome targets presented by cells in mitosis at metaphase or anaphase. Chromosomes are not only the bearers of hereditary

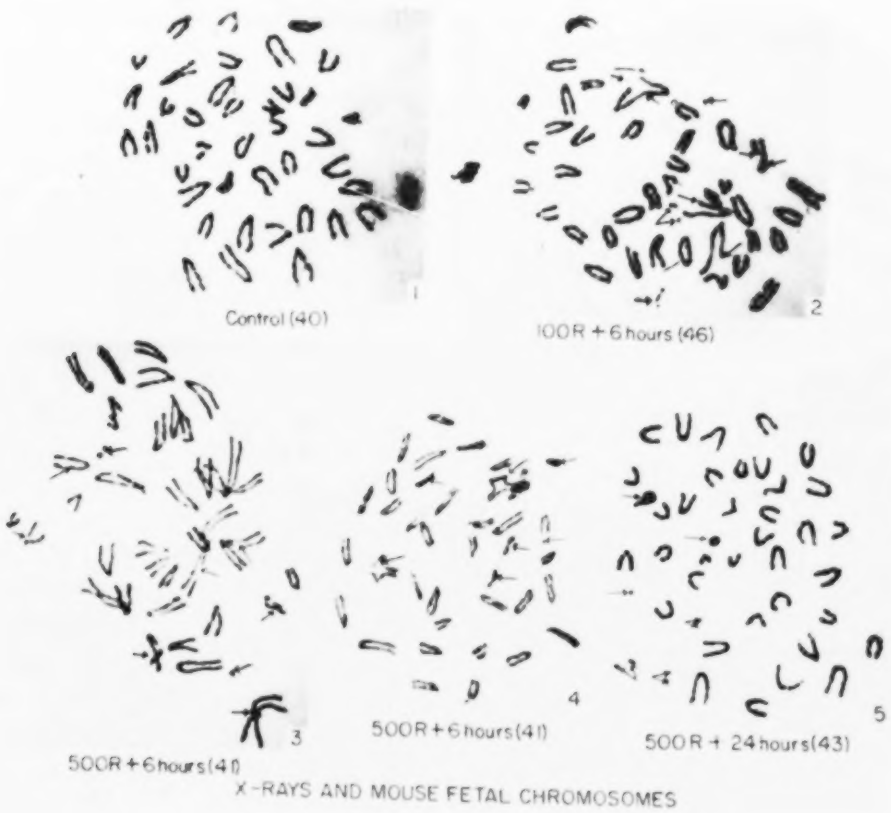
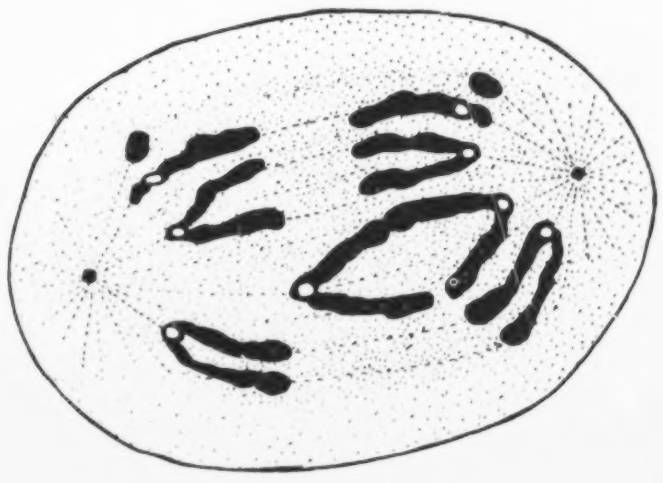


Fig. 2 The effect of x-rays on the chromosomes of the fetus is illustrated in these photographs. The control (upper left) shows the 20 pairs of mouse fetal chromosomes all intact. All other photographs show damaged chromosomes: fragmented, deletions, rings, and general aneuploidy. It was found that about 6 hours after x-irradiation the damage was maximum and after this many of the damaged cells were removed, probably by phagocytosis.

influences (genes), but they most certainly control embryonic and fetal development. At present, it is not exactly clear how this control is achieved. Thus, if chromosomes are radiation insulted prior to the expression of their potential for control in development, it is natural that any damage incurred would seriously affect such development. This is one highly probable way of causing congenital anomalies. Such anomalies are unlikely to be produced after the organ has been differentiated and formed.



Anaphase with non-disjunction

Fig. 3 Since chromosomes in an x-ray field of ionizing radiations become sticky . . . this drawing shows how non-disjunction could occur, simply by having two members of a pair fail to separate because of the radiation-induced stickiness.

I am thus suggesting that it is perfectly logical that first the embryo and, later the fetus, will exhibit high radiosensitivity. This is because of the high level of mitotic activity and is vital because the chromosomes which are so directly responsible for normal fetal development are so vulnerable to radiation exposure during mitosis.

Congenital anomalies must be distinguished from hereditary anomalies since they are **not inherited** and are always due to some traumatic situation encountered during development. Penetrating ionizing radiations are such a traumatic insult to any embryo or fetus that it is now possible to produce, to a high degree of predictability, specific anomalies when, for example, a certain dose of x-rays is delivered to the embryo or fetus at a certain stage of development. But even with such predictability, the anomaly, though tolerated, has no relation to the germ cells and is never passed along to the next generation. It should be emphasized that no anomaly produced or induced by ionizing radiations is peculiar to such radiations, but has been seen following other traumatic impositions or for no definable reason. Thus, any radiation induced con- but at rather high levels, and at the various abnormal development following interruption by ionizations of the normal chain of developmental events. If induced congenital anomalies were inherited, radiations would be even more disastrous to civilization, for there would result such a tremendous variety of bizarre types which could be propagated. Thus, failure to reproduce such anomalies and sometimes even to survive, places limits on the damaging effects of ionizing radiations on the embryo or fetus. These statements do not preclude genetic or mutational effects mediated through exposed germ cells, but this aspect is not included in this discussion.

The embryo or fetus is a mosaic of differentiating organ systems and, at any specified moment, some organs will be more active than others in their development. For this reason exposure at different stages of gestation will elicit different reactions to ionizing radiations in the terms of congenital anomalies. However, since it is not the primitive undifferentiated tissue nor the fully formed organ which is so radiosensitive, but rather the intermediate or transitional stage, it is possible to plot a map of development which is based upon the effect on the various organ systems in relation to the point in the gestation period during which the organism was exposed. For example, to produce abnormal eyes in the mouse, it should be x-rayed between the 9th and 12th days of gestation. This point corresponds roughly to 25-37 days for the human. Exposure at this point of the embryo's development does not exclude effects on other organs, nor does it

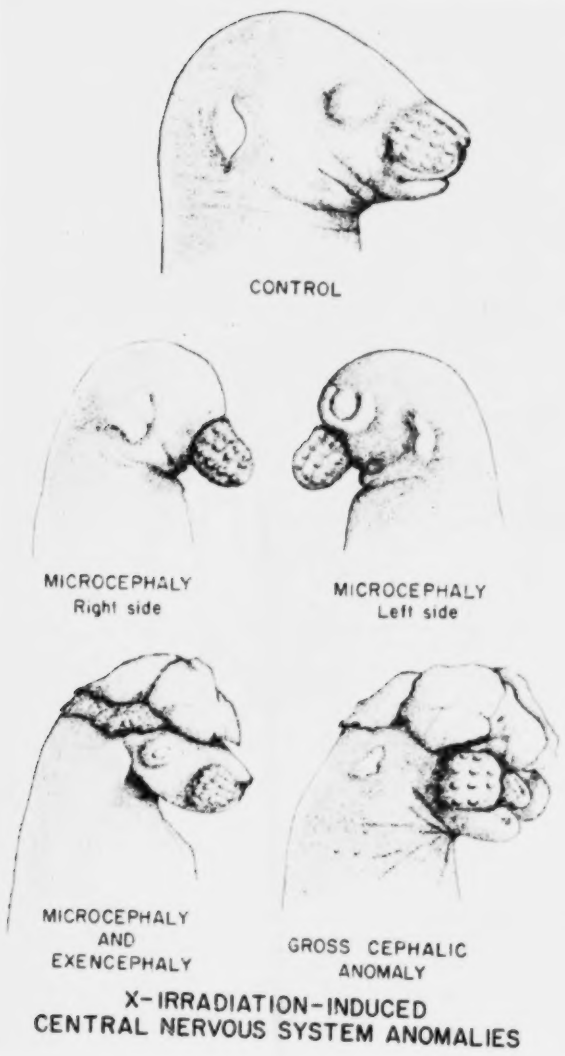


Fig. 4 Drawings of some of the cephalic anomalies caused by x-irradiation of the mouse embryo or fetus prior to the completion of development of the central nervous system. The control (top) shows the normal bilateral symmetry and head contour and all those x-rayed (lower pictures) show reductions in head size and various anomalies such as anophthalmia; microphthalmia, exencephalia; and microcephalia. The most pronounced effects of embryonic and fetal x-irradiation appear to relate to the central nervous system.

guarantee any specific defect in the eye development. There will be different responses between individuals in any litter, and, in fact, between the left and the right eye of any single individual. However, by x-radiating mouse embryos and fetuses for brief periods, but at rather high levels, and at the various periods in gestation, it is possible to identify and map out the time period of each organ's differentiation. To state it otherwise, and more inclusively, only a differentiating tissue or organ (transforming from primitive to formed) can react to ionizing radiations by producing a congenital anomaly, so that x-irradiation at any point in the gestational period will identify those tissues and organs which are in the process of transformation (or what is called differentiation). It is important to make one more statement! Even though a particular litter is exposed to a uniform field of highly penetrating radiations, this will not insure uniform response of the litter members because no two members have the identical hereditary potential. Thus, rats which have been exposed at 9 days have been observed to develop one normal and one reduced eye, while another member of the same litter had no eyes at all. The major concept which is being stressed here is that eyes are affected because they were in the process of forming (differentiating) at the time of exposure, but that even individual eyes in the same animal will respond with respect to hereditary susceptibility.

It is in light of these facts that I feel a strong need to caution radiologists about the dangers inherent in exposing the human female pelvis during the first 6 weeks after conception. In order to avoid the possibility of irradiating a female who has an unrecognized pregnancy, I recommend limiting diagnostic and therapeutic radiation to the pelvis of females of reproductive age to the first 9 days after the onset of menstruation. . . . unless the patient is experiencing a medical emergency which leaves the radiologist with a difficult determination in weighing the potential benefit to the patient against the potential risk to the embryo or fetus.

Before elaborating on the gamut of congenital anomalies that result from exposure of the embryo or fetus to ionizing radiations I must emphasize that such exposures can and do kill the rodent embryo or fetus, or can cause such damage that postnatal survival is limited. Pre-implantation exposure is the most radiosensitive and such zygotes and embryos are generally killed outright, leaving no residuum. Except for histological and cytological evidence for this, the major clue is that litter size is reduced below the average. If a later stage

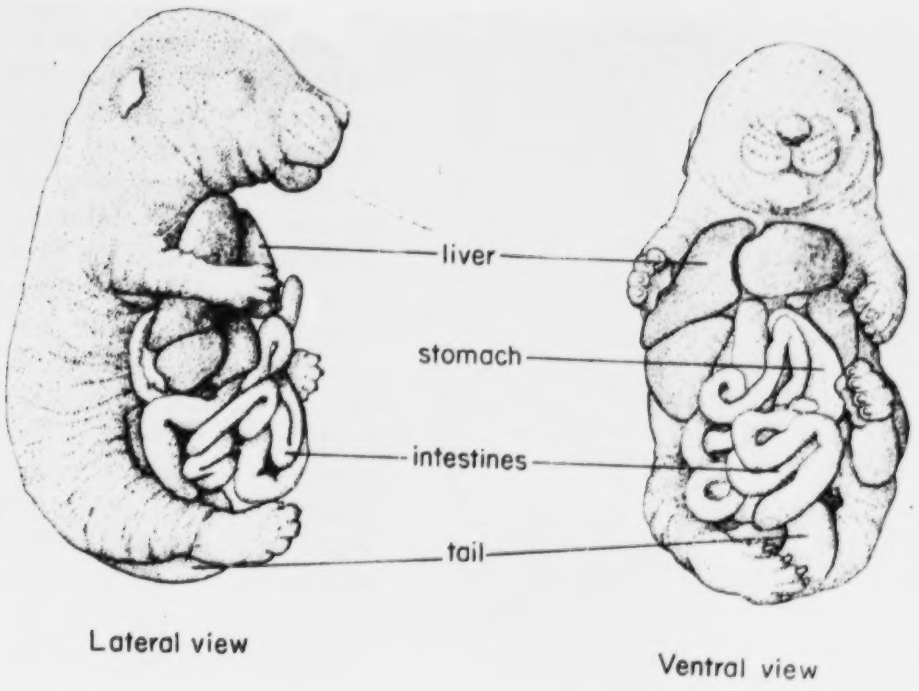


Fig. 5 Drawings of a mouse fetus at 18 days gestation, which had been exposed to 200 R of x-rays on the seventh day of gestation, long before any organ differentiation had occurred. The viscera normally begin to develop more or less outside the body, but are usually incorporated into the body. This "apparent" evisceration may be caused by ionizing radiations, as in this case.

is exposed, such as between days 5 and 11, there may result a dead fetus which is retained until the normal time for delivery of the surviving siblings. Usually such a dead fetus (stillbirth) is lost if delivered so that evidence for fetal death is found by dissecting the gravid uterus of the mouse at 18 days before the expected delivery or by delivering the litter by Cesarean section. In this way dead fetuses can be identified. If they are delivered naturally, the mother generally devours them immediately, hence they cannot be counted. But ionizing radiations can cause such deviations in development as to kill prior to the time of delivery, in the fetal stage. Finally, anomalies can be induced which will not allow postnatal survival even though delivered. It is likely that the same situation holds true for the human, i.e. that intolerant levels of ionizing radiations, when given to the zygote or embryo before implantation, may kill it outright. In these cases it is never even recognized as a conceptus. When the gravid human pelvis is x-irradiated between 10 and about 42 days, one would expect congenital anomalies to be detected when the exposures are above 25 R. After about 6 weeks the survival is better, structural anomalies are less likely to occur, and yet one should still expect functional anomalies when the exposure is above the 25 R level. This level is selected because it is known that neuroblasts are vulnerable at this level and such transforming cells are present throughout all human gestation and for several weeks thereafter. Thus, the extreme effect of such radiations is lethality and the threshold level of any effect is 25 R or below.

Among the congenital anomalies caused by

radiations of the developing mouse there are at least fifty varieties, the majority of which have to do with the central nervous system.

However, there are anomalies of the cardiovascular, gastrointestinal, and skeletal systems as well, and anomalies of every organ system. But they have different levels of tolerance and hence different effects on survival for the exposed individual. Some examples of tolerable anomalies are cataracts, stunting, and aging and some types of cancer which can be deterred, and others (leukemia) that are lethal. Every human congenital anomaly attributed in the literature as due to in-utero x-irradiation has been duplicated by x-irradiation of experimental animals, if such a duplication is conceivable. The effect on mental acuity or I.Q. would not be testable in animals. At lower exposure levels, or when the exposure occurs at later stages of development, the results are more likely to be at the functional level. They can be exhibited by electroencephalographic, electrocardiac, electroretinographic, or even electromuscular recordings. These findings have been well documented in rats and could possibly be true also for the human and yet they have never been detected, simply because it is impossible to experiment with the human, to have controls, or to have good enough statistics to make such statements incontestable. For example, if it should be true that x-irradiation during the 8th month of gestation of the human to 200 R would reduce its ultimate I.Q. by 40 points, how could this ever be detected? While we can never extrapolate from man to man, or from animals to man, our research results with other mammals can only be qualitatively suggestive for the human. Human behaviour could well be affected by x-irradiation of the embryo or fetus (and is quite probable) since it has been demonstrated in other mammals.

The third question dealt with the possibility of preventing radiation induced congenital anomalies when the pregnant animal (or woman) is exposed. Obviously, if the gravid uterus is shielded against the ionizing radiations, the embryo or fetus will be protected as long as the somatic reactions of the mother do not produce toxins that would be diffusible to the fetus through the placenta, or otherwise curtail her physiological functions necessary for the survival of the fetus. Only direct radiations can have effects on the fetus. There seems to be slight evidence that anoxia and spleen or bone marrow homogenates, or even possibly some of the so-called radioprotective agents such as AET, might have some protective value for the fetus when it is found to be in a radiation field, but this has not yet been statistically or satisfactorily demonstrated. Thus, it is best **not** to expose the human zygote, embryo, or fetus to any **unnecessary** ionizing radiations until there is considerably more documented evidence.

I have already touched upon the possibilities of human exposure through both diagnosis and therapy in sufficient detail to make it clear that such exposure ought to be limited to those situations in which the mother's health and survival are involved. Very little is known about the effects on the human embryo or fetus but, if animal experiments are any guide, it would pay us to be exceedingly cautious. It is known, for example, that mice are 15 times more radiosensitive than the experimental fruitfly in the production of mutations by ionizing radiations. No one knows whether the mouse or the human germ cells are more radiosensitive. The radiological literature contains abundant references to human babies that exhibit congenital anomalies which have had a history of x-irradiation while in utero. Such references are isolated, consisting of single cases, and often without adequate documentation with respect to the exact exposure at the level of the fetus, and the time of exposure, so that at the moment it is impossible to be dogmatic or positive about the effects of such radiations on the human fetus. In the interest of information in this regard, since human applications of such research findings are of importance, I will append a list of the references on human fetal effects to this paper and hope that, as the volume of such references is increased, and the information is more complete, it will ultimately be possible to make statistically accurate statements. With the knowledge that about 5% of all human

births bring with them congenital anomalies of unknown origin, it will probably never be possible to ascribe any particular anomaly to prior x-irradiation. Nevertheless, it would be inaccurate to suggest that human anomalies cannot be produced by x or any other type of irradiation which brings about ionizations in tissue at least until there is a vast amount of more reliable data. It would help if there were a repository for such data, a laboratory where irradiated human tissue studies could be made, and if more radiologists would be alert to the importance of reporting such information from their practices.

Ionizing radiations affect biological systems immediately, irrevocably, and more drastically than any other known physical agent. Such effects are more serious in a zygote, embryo, or fetus than in adult tissues for two reasons. First, the cells are more radiosensitive by virtue of their mitotic and differentiating activity and second, because such cells are the progenitors of vast numbers of descendent cells which will comprise the newborn and adult. Thus, while discussion of the biological effects of such radiations should encompass the developmental stages, it must be emphasized that these stages have a high level of sensitivity and the responses are likely to be more permanent and significant in the life of the individual. Some general conclusions can be offered.

The effects of exposure to ionizing radiation discussed in this paper are illustrated in Appendix 1 and outlined in Table 2 for ready reference. Appendix 2 is an extensive bibliography which has been added as a supplement to this paper in the hopes it will prove a benefit to those who desire to pursue the recorded cases of fetal exposure to ionizing radiation in more depth.

Table 2 Anomalous Conditions Attributed to X-Irradiation of the Mammalian Embryo or Fetus

Abdominal Herniation (50)
Ageing (12.5)
Amelogenesis
Anemia, Aplastic
*Anencephalia (100)
*Anophthalmia (50)
Anus, Imperforate (200)
Aortic Arch Atresia (200)
*Aqueduct, Narrow
Bones, Absent
Bone Anomalies, Var. (100)
*Brain Anomalies, Var. (100)
*Brain Weight Reduction
*Capsule, Internal Distorted
Cardio-Vascular Anomalies (100)
*Cataract (200)
*Cerebellar Pattern Defective
*Cerebral Atrophy (100)
*Cerebral Cortex Reduction
*Cerebral Vesicle Degeneration
*Choroid Plexus, Atrophy (100)
Cleft Palate (100)
Cloaca, Persistent (100)
*Coloboma (100)
*Cordis, Ectopia (100)
*Corpora Striatum, Anomalous (100)
*Corpus Callosum, Agenesis (250)
*Cortical Degeneration
*Cortical Rosettes
*Cranial Blisters
Cryptorchidism (100)
*Cyclopia
Dextrocardia (50)
Digital Anomalies (Poly-, Polysyn-, syn, Macro-, Micro-, Brachy-, Oligodactylias)
Dwarfism
*Ear, Middle Retardation
Edema (100)
*Encephalocoele (50)
Endocardial Cushion Anomalous
*Exencephaly (Pseudencephaly, Cranioschisis, Cerebral Hernia) (15)
Eyelids Open
Face, Cleft (150)
Feet, Overgrown & Deformed
Genetic, Various (12.5)
Gonad Absent or Degenerate (100)
Growth Retardation (12.5)
Harelip (150)
*Head, Abnormal Shapes (Narrow)
*Hemispheres, Widening of Interspaces
Hernias:
*Brain (Encephalocoel, Meningocoel, Hydro-encephalocoel, Hydro-meningocoel)
Diaphragmatic
Thraco-Abdominal (Visc. Eversion)
*Hippocampus, Pyramidal Cell Layers Displaced (250) & Widening of Hippocampal Spaces (250)
Hydrocephalus (25)
*Hydromylia (25)
Hydronephrosis
Hydroureter
*Hypermetropia
*Idiocy
*Internal Capsule Anomalous (200)
*Iris, Narrow
Kidneys, Absent (100)
Kidneys, Fused (100)
Lethality, Various Causes
*Lens, Absent
*Lens, Dislocated (100)
Leukemia
Limbs, Malrotated (100)
Lip, Cleft (100)
Liver, Anomalous (100)
Liver Necrosis (100)
Mandibular Shortening (50)
Maxillary-nasal cleft (100)
*Medulla, Small (Reduced)
*Medullary Rosettes
Metaphysis
*Microcephaly (100) (Micrencephaly)
*Microcornea
Micrognathia (100)
*Microphthalmia (75)
*Neurological Deficits (25)
*Neocortex, Defective
*Odontogenesis Imperfecta
*Optic Nerves Absent (200)
*Optic Nerve Atrophy (200)
*Otocephalia
Palate, Cleft (100)
*Porencephaly
*Pseudencephaly (25)
*Retinal Cell Layer Reduction (50)
*Retinal Rosettes
*Retinoblastoma
*Rosette Formation in CNS (12.5)
Scoliosis (50)
Situs Inversus (100)
Skin Pigment (Hyper or Hypo)
Snout, Beak-Like (50)
*Spina Bifida (50)
*Spinal Cord with Gross Curvature (25)
*Spinal Cord, Herniated (150)
Spinal Cord with Malclosure
Sterility (30)
Sternebrae Absent (200)
*Strabismus
Stunting, Uniform Reduction
Tail, Short, Deformed, Absent
*Telecephalon, Retarded
*Telencephalon, Univentricular
Thyroid Anomalous
Thoracic Herniation
Tibia, Exostosis on Prox. Pt
Tumors (2 R = Doubling Dose Stewart?)
Urino-Genital Anomalies
*Ventricular Dilatation
*Ventricular Wall & Cortex, Multiple Heterotopias
Ventriculocoele
Functional:
*Audiogenic Seizures - 1R
*Motor Learning - (100 R)
*Motor Strength (50 R)

(Note: Numbers in parentheses are x-ray exposures in Roentgens reported to have caused the particular anomaly. Asterisk indicates neurological anomaly.)

CONCLUSIONS

1. The embryo or fetus of any species is more radiosensitive than is the adult into which it develops. The range of reaction is from lethality to survival with various levels of congenital anomaly development.
2. It is true that the actively developing organism has certain powers of survival even with congenital anomalies, and such anomalies, when induced by irradiation, are never inherited. The adjustment involves the ability to discard or to phagocytize the necrotized cells, leaving those cells which are either not affected or affected to a tolerable degree, out of which a stunted, but otherwise normal individual can develop.
3. Zygotes, embryos, or even fetuses can be killed by x-radiation in utero and the dose to achieve this varies with gestational age. It is not linearly increased with developmental stage, but shows peak points of sensitivity.
4. The types of anomalies produced do have some relationship to the time of x-irradiation of the zygote, embryo, or fetus. Peak sensitivity appears to be at about days 8-9 which corresponds in human development to days 20-25. However, since congenital anomalies can be produced through day 14 in the mouse, it is believed that the human conceptus should be protected against any radiation insult, if possible, through the first 6 weeks of development after which such structural anomalies are probably less likely to be produced. Functional anomalies are more difficult to identify and evaluate.
5. The variations in response of closely related strains, siblings in any litter, or even bilateral parts of a single fetus indicate that, while the radiation field may be uniformly penetrating, the biologically reacting system is not uniformly responsive and, that bilateral organs presumably developing at the same time and rate may show wide deviations in response such as one eye being anophthalmic and the other apparently normal. This may indicate a threshold but, more likely, it is genetic variability in radiosensitivity even within a single individual.
6. There is no evidence that x-radiation can accelerate proliferation of cells or stimulate development and differentiation. Regeneration by proliferation has never been seen.
7. The chromosome is probably the chief target of ionizing radiations and, since the intact chromosome is so important to normal ontogeny, the high radiosensitivity of the chromosome in developing tissue probably relates to the peculiarly high incidence of congenital anomalies following x-irradiation of the zygote, embryo, or fetus.
8. The developing organism, from zygote to newborn, probably reveals more information relative to basic radiobiological responses than any other stage of life or of any tissue or organ. The ultimate explanation of congenital anomaly effects of ionizing radiations will probably rest with chromosome studies and revelations of the electron microscope of cells which have been so altered by ionizing radiations that they can be shown to affect adversely the development of the organism.

*Based on work performed under Contract AT-(30-1)-2740 for the U. S. Atomic Energy Commission

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*These references are not made in the text of this paper in order to (1) conserve space and (2) to avoid distraction from the thesis being developed. Nevertheless, all are sources for the various statements made and are therefore important. Any interested reader can identify a particular research pertinent to any statement, or his particular interest.

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APPENDIX 1

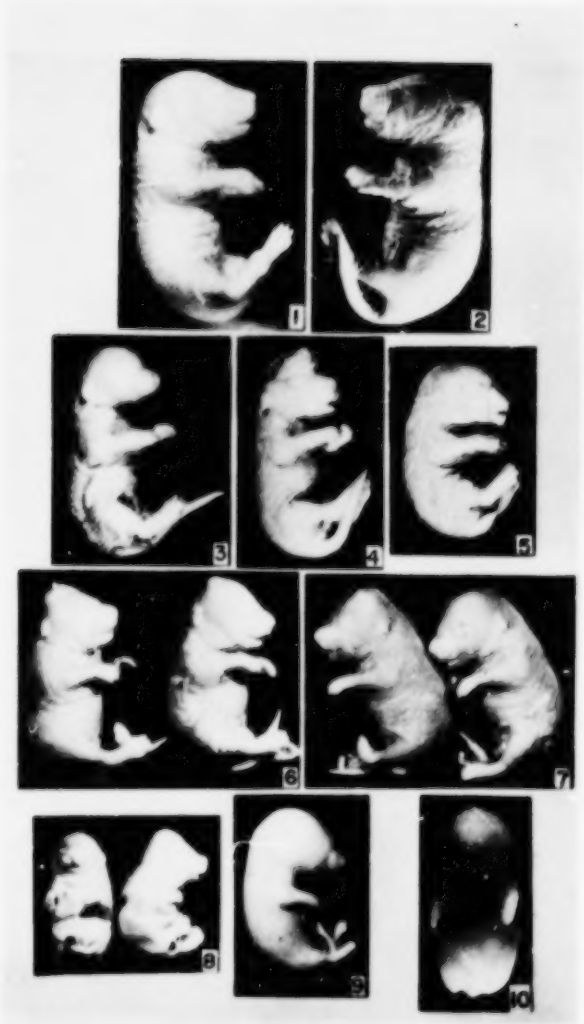


Fig. 6 Photographs of living specimens of mice at 18 days gestation, delivered by Cesarean section, showing a variety of congenital anomalies all resulting from x-irradiation during development. Figs. 1, 2 are two views of the control. Note that it is larger than all those x-rayed. All other photographs show various degrees of head anomalies, and 9, 10 are without sense organs or mandibular differentiation. Every anomaly seen following embryonic or fetal x-irradiation has been produced by other insults so they cannot be regarded as radiation specific.

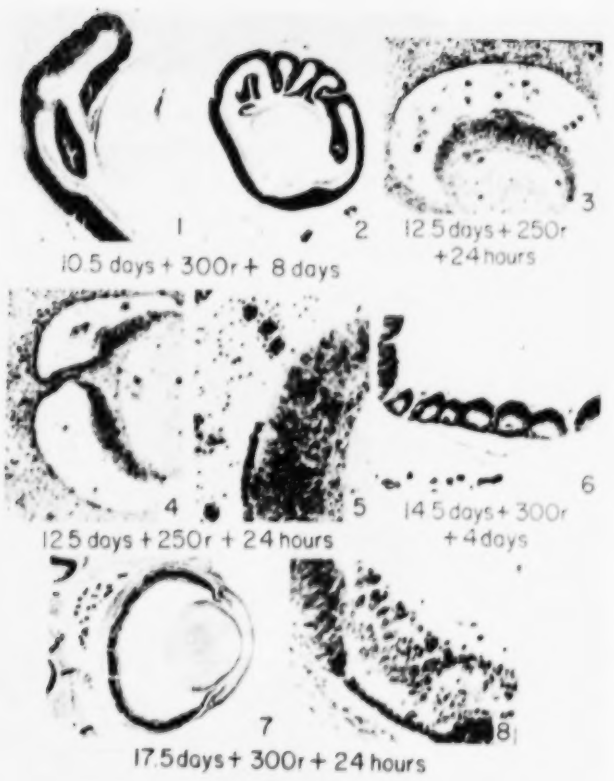


Fig. 7 Histological sections of eyes of mice x-rayed in utero at 10.5, 12.5, 14.5, and 17.5 days gestation and sacrificed for study at various intervals thereafter. Note disruption of the retina with folds resulting from attempts on the part of the developing retina to reform from undamaged neural cells. Rosettes are a common structural sequela of such irradiation, as noted in figs. 6 and 7; and abundant phagocytes devouring the dead cells as seen in figs. 3, 4, and 5.

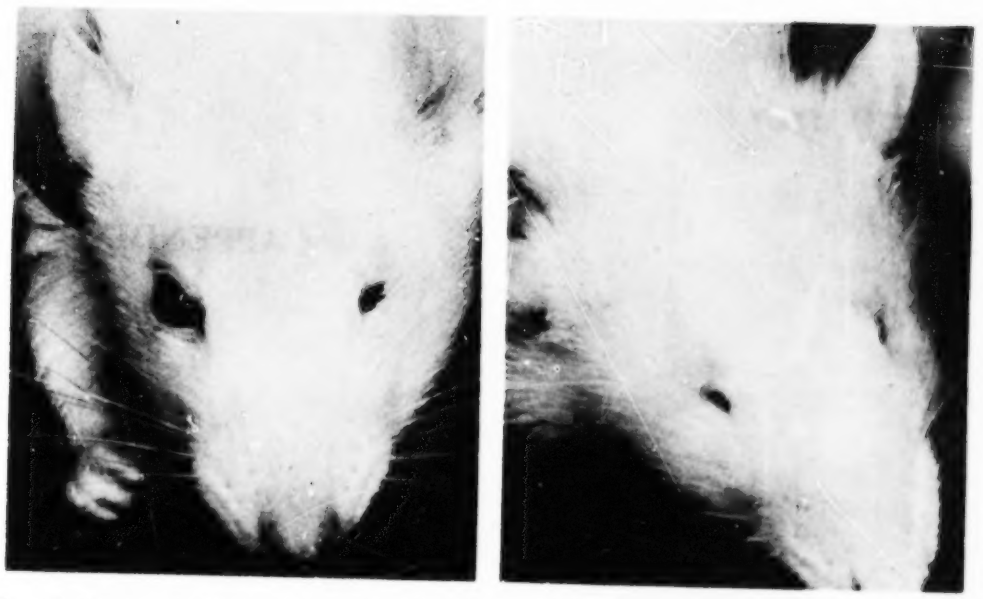


Fig. 8 Two rats from the same litter, exposed at 9 days gestation to 150 R x-rays. Note how different the two have responded to the irradiation. On the left the rat has a normal right eye and a microphthalmic left eye. In the other rat, to the right, both eyes are anophthalmic and yet the two rats were litter mates and presumably exposed to the same field of ionizing radiations.

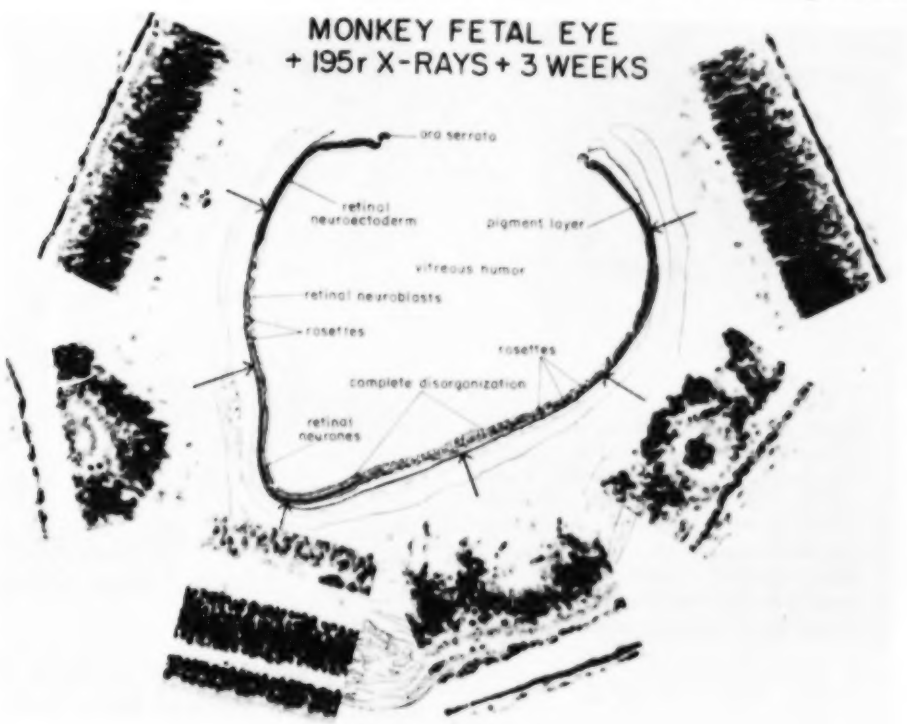


Fig. 9 A composite drawing and photographs showing regional differentiation of the monkey fetal retina at a specific time in gestation. The posterior segment of the retina differentiates first and, in this case, is thereby radioresistant. The intermediate zone is in the process of differentiating, hence is highly radiosensitive. The anterior zones, near the ora serrata, are undifferentiated and hence are radioresistant also. The photographs are of actual histological sections from corresponding regions of the diagram and serve to illustrate the above statements.

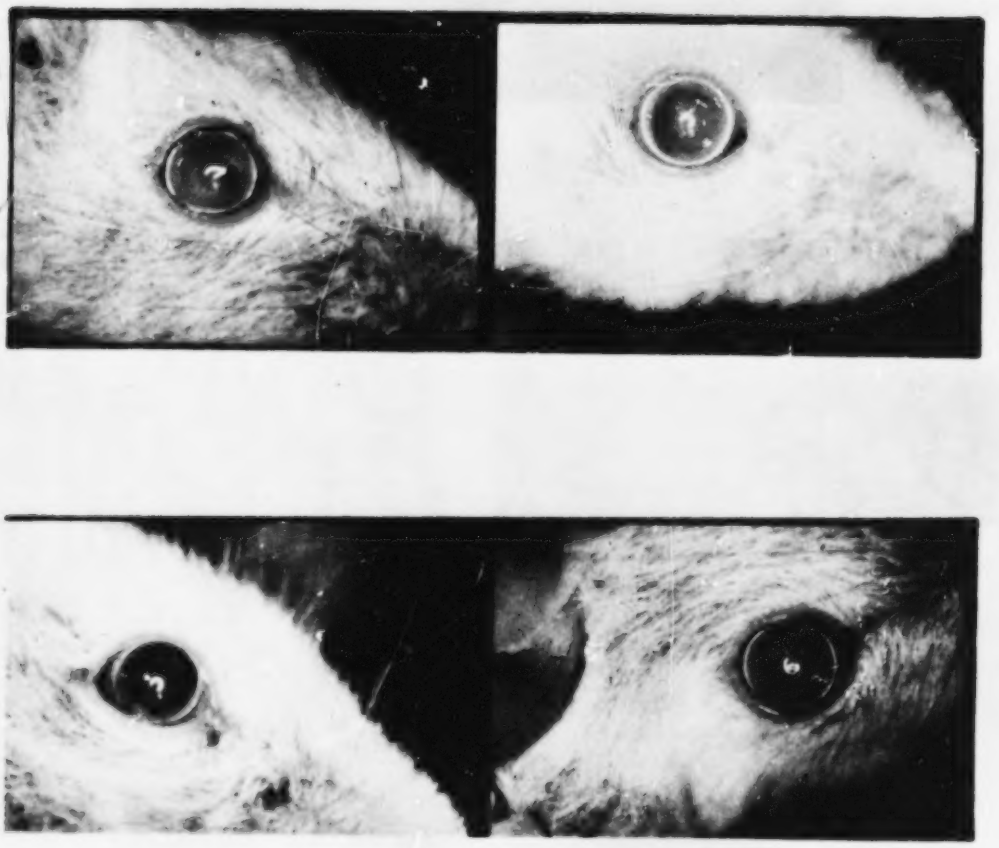
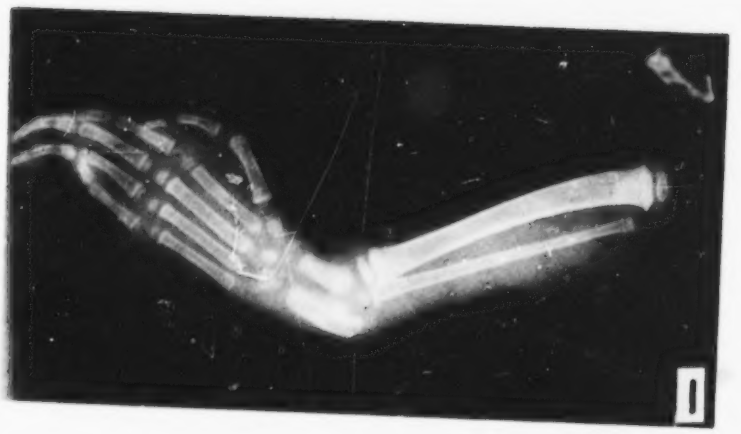
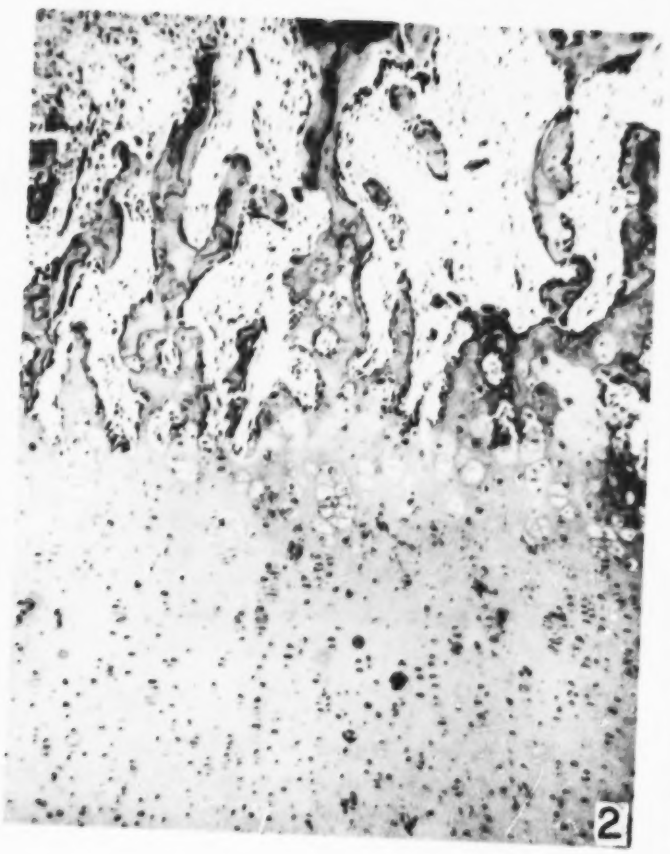


Fig. 10 Cataractous eyes of mice x-rayed in utero to only 100 R at the time of fertilization. These pictures indicate that congenital anomalies can be produced by exposure even before the organs begin to differentiate.





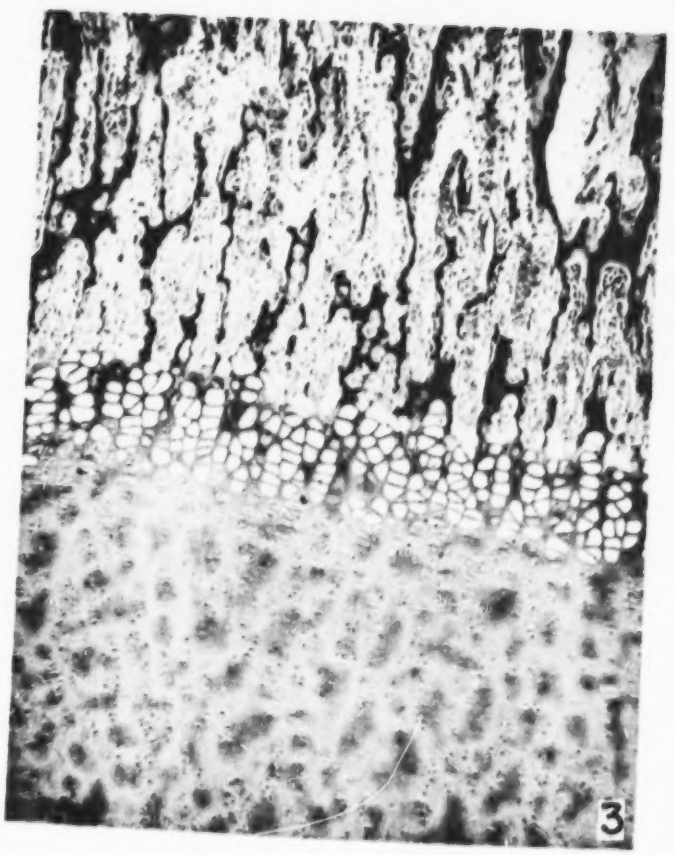


Fig. 11

1 - Radiogram of lower leg of monkey x-rayed to 200 R at fetal age of 130 days and sacrificed 36 days later, or 12 days after birth. Note growth arrest lines in the proximal and distal ends of the tibia and several of the digits.

2 - Distal epiphysis of the femur of monkey fetus which had received 400 R x-rays at fetal age of 90 days and was sacrificed at fetal age 125 days, or 35 days later. The epiphyseal structure is badly disrupted.

3 - Distal epiphysis of femur of monkey fetus which was an unirradiated control of about the same age as that shown in fig. 2.

(Sections and study made with assistance of Dr. H.Q. Woodward)

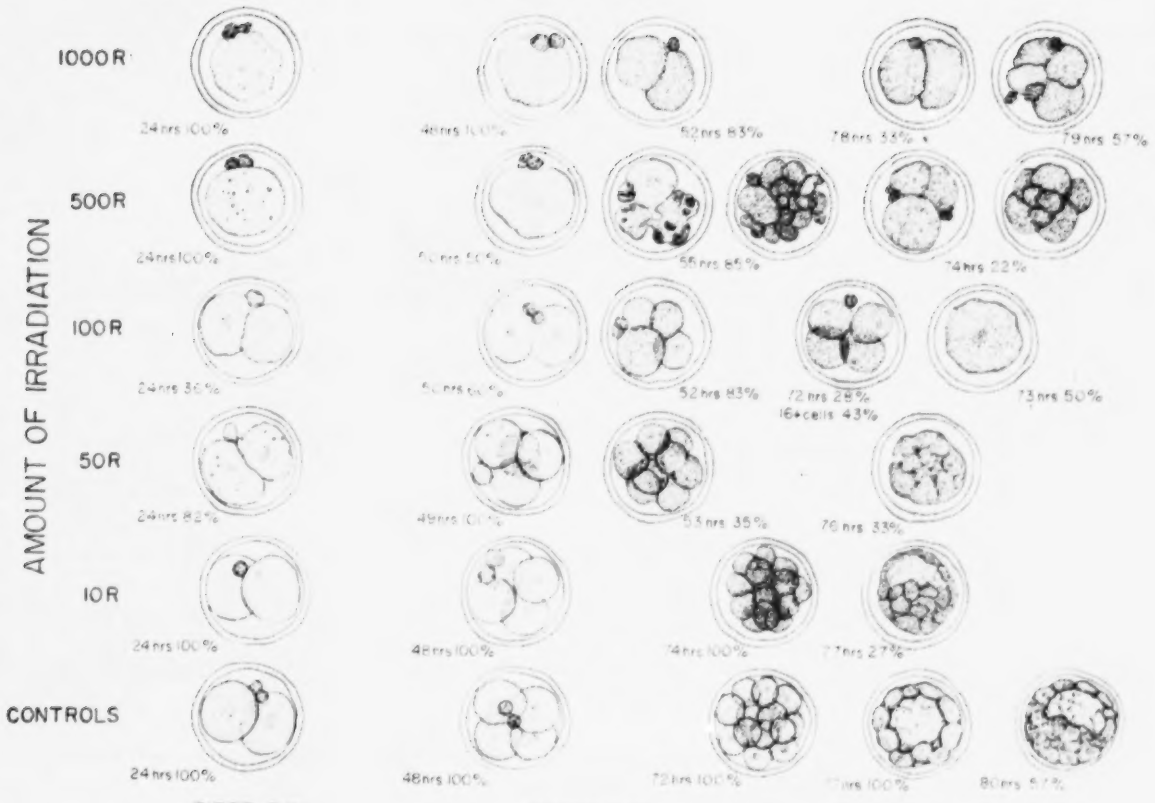


Fig. 12 This drawing is an attempt to depict the changes one sees in the zygote and early embryo of the mouse after exposure to various levels of x-rays (10 R to 1,000 R) at 7 hours after fertilization, the time of maximum sensitivity. The controls are along the bottom series. It can be noted that as the dose is increased (above) that the abnormalities are more frequent until development is stopped completely by exposures of 100 R or more. Development is damaged by exposures of 50 R and retarded and made abnormal even at 10 R. This drawing gives no statistics, but is qualitatively significant, indicating the method of retarding and killing the early mouse embryo. (Drawings by R. Van Dyke)

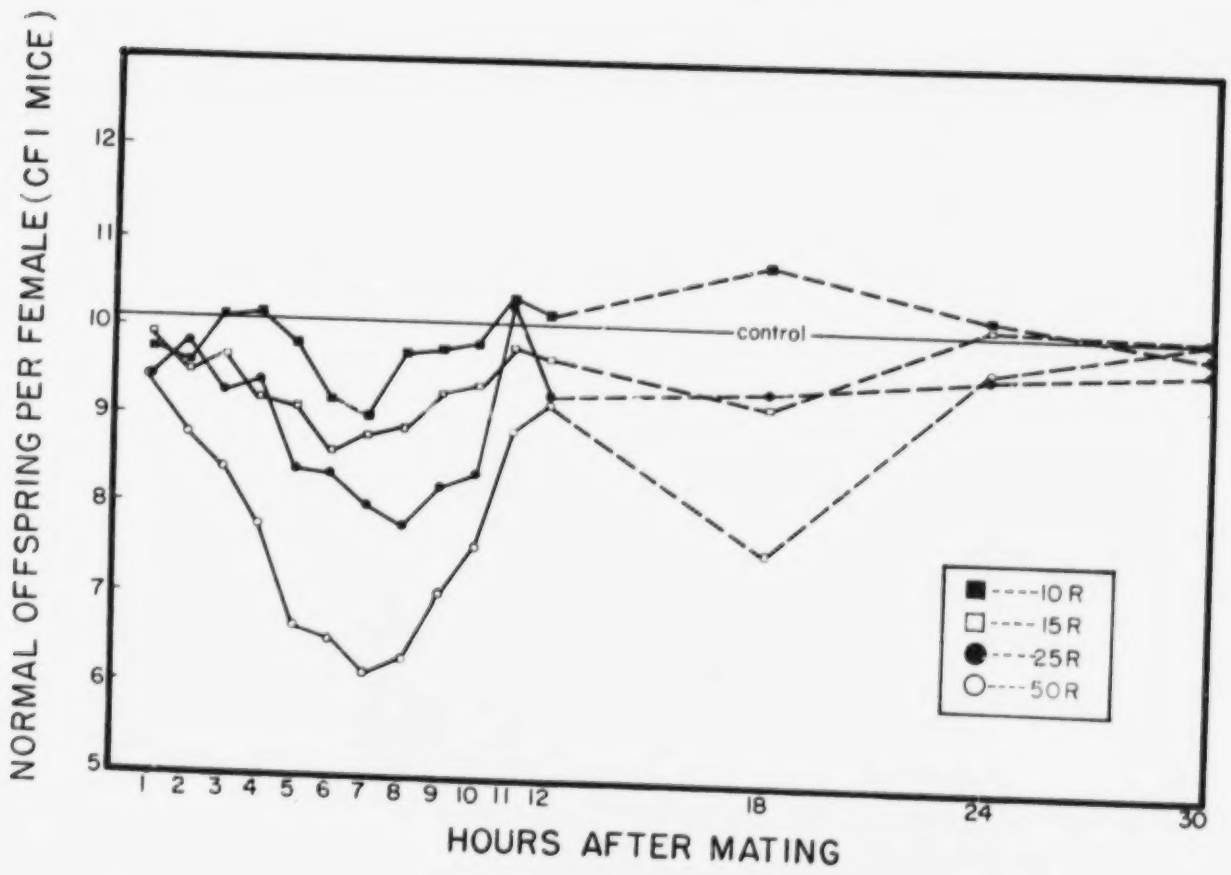


Fig. 13 In a study involving 34,804 x-rayed mouse embryos compared with 9,950 parallel controls it was found that at 7 hours after mating there was an appreciable reduction in the litter sizes due to killing of the embryos when the exposure was as low as 10 R x-rays. Further reductions were caused when the doses were 15, 25, or 50 R. Thus, even before the first cleavage of the fertilized ovum, the radiosensitivity was demonstrated at 10 R. This is within the range of possibility from diagnostic radiology. This is the time when the two pronuclei (from ovum and from sperm) are approaching each other to accomplish syngamy. (from Rugh, Wohlfromm & Varma 1969)

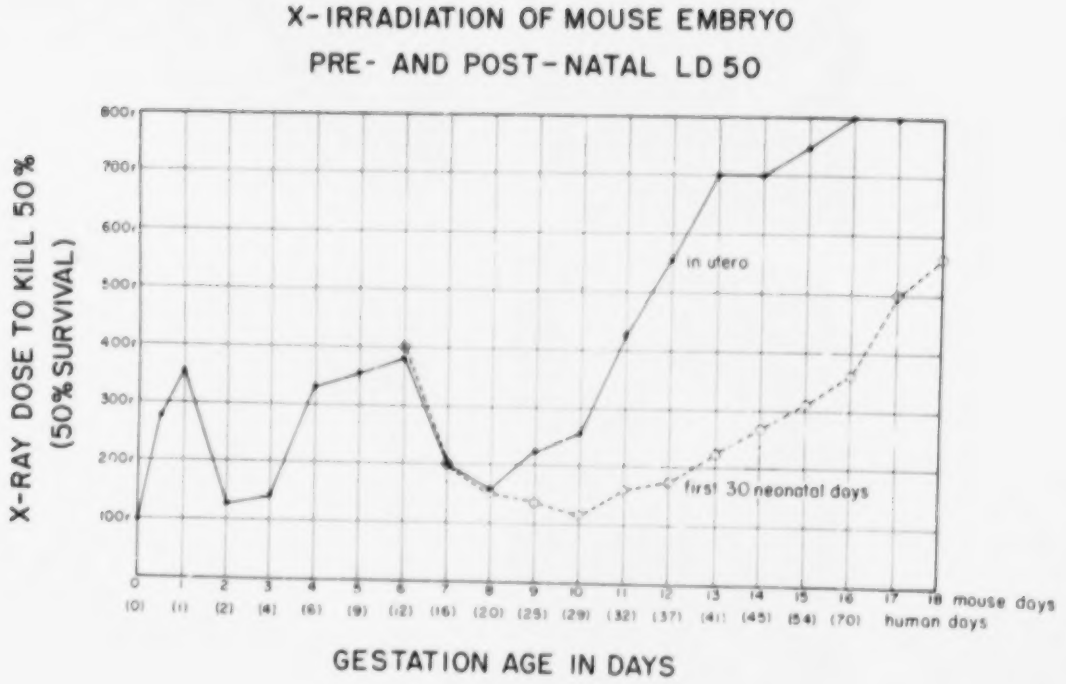

X-IRRADIATION OF MOUSE EMBRYO
PRE- AND POST-NATAL LD 50
X-RAY DOSE TO KILL 50 %
(50% SURVIVAL)
800r
700r
600r
500r
400r
300r
200r
100r
in utero
first 30 neonatal days
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 mouse days
(0) (1) (2) (4) (6) (9) (12) (16) (20) (25) (29) (32) (37) (41) (45) (54) (70) human days
GESTATION AGE IN DAYS

Fig. 14 Graph showing the amount of x-ray dose which would kill 50% of the exposed embryos or fetuses in utero (solid line) and 50% of those that are delivered within the first 30 days of life (broken line). Note that there is no linear increase in radioresistance with gestational age, although the later stages are the more resistant. Note also that, if the 8 day fetus is exposed to 160 R x-rays, that 50% will die before the time of expected birth and another 50% during the first 30 days, leaving a net 25% to live. Thus this rather low level of exposure is devastating when given at 8 days development. (Rugh & Wohlfromm 1965)

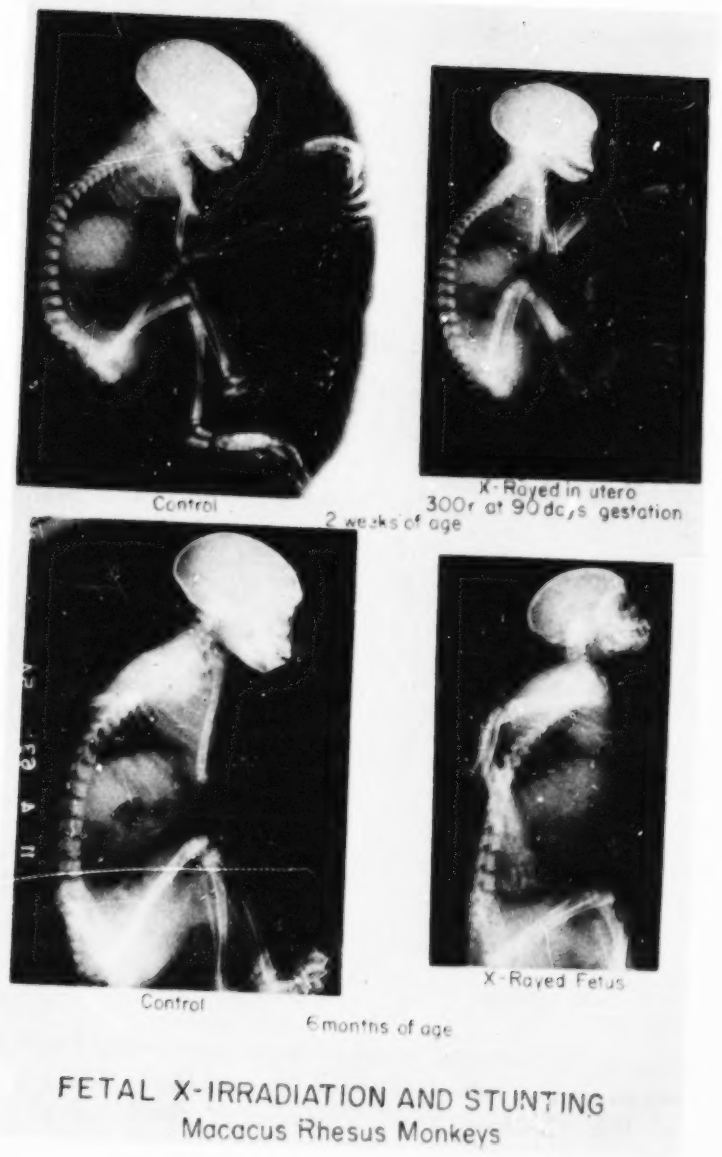


Fig. 15 The control monkey is at left, at 2 weeks (above) and at 6 months (below). To the right is the monkey x-rayed as a fetus at 90 days gestation. Note the stunting, evident even at 2 weeks (above) and maintained at 6 months (below). This stunting was rather balanced in that all organs measured and weighed were reduced, but the fact the organism survived for 23 months indicated that, in spite of such stunting, without a control with which to compare, it well might have been regarded as "normal".

Fig. 16 Mice at one month of age. The control mouse is on top and below is a mouse from a litter which had been exposed to 150 R of x-rays at 14 days gestation. The exposed mouse shows topographical reduction, but apparently normal relations of all developed bones. Should the lower or x-rayed mouse be examined independently of the control, it would likely have been considered normal.

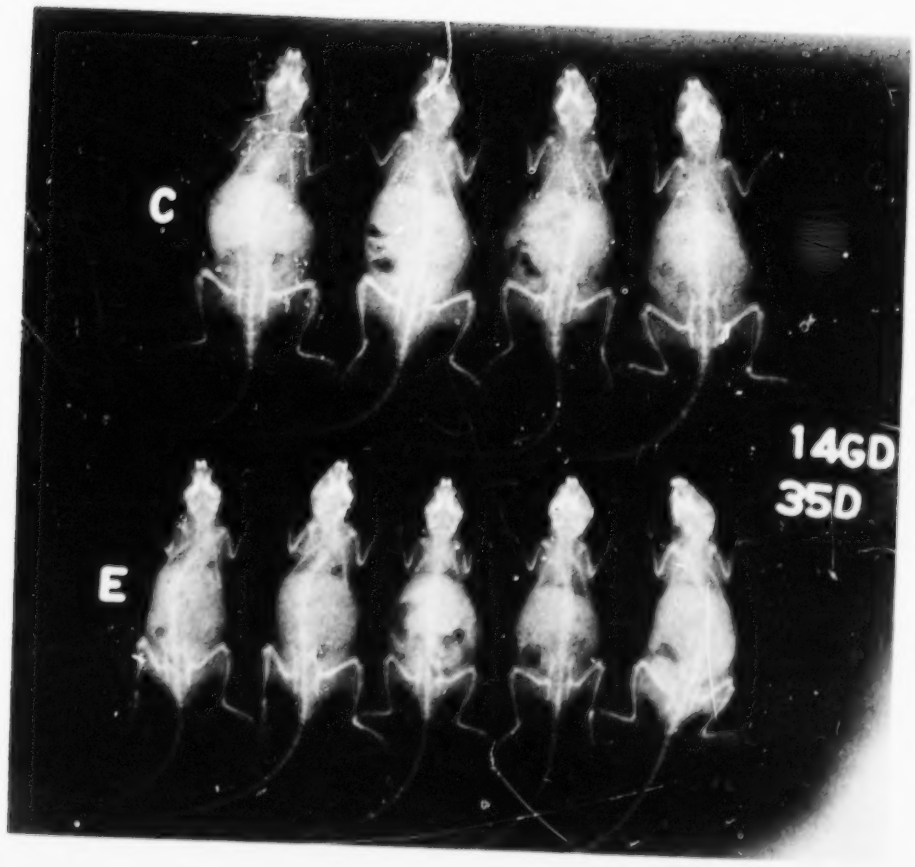
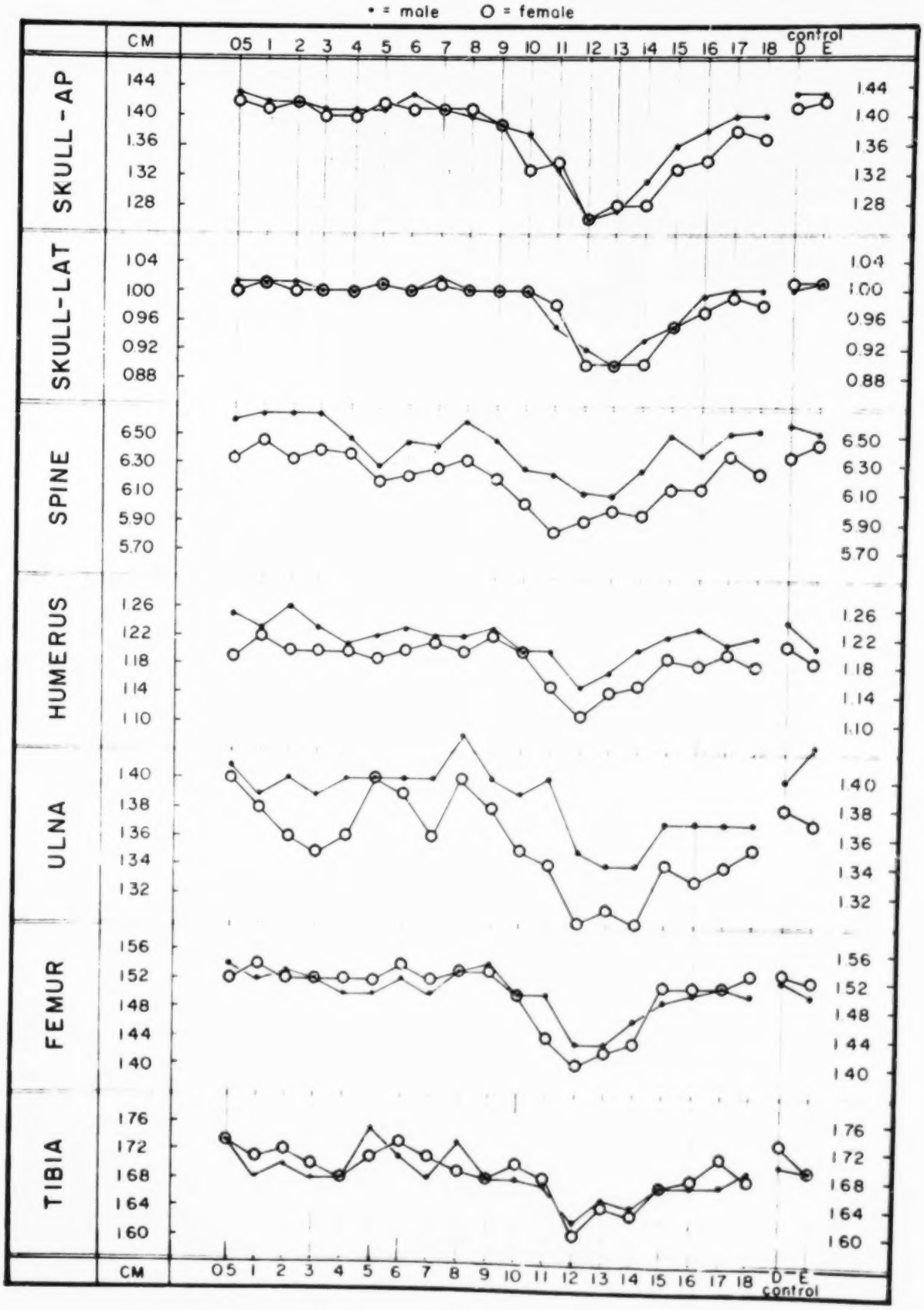


Fig. 17 Entire litters of mice at 35 days, showing the controls (above) and the x-rayed experimentals (below) which had received 150 R x-rays at 14 days gestation. Note uniform stunting with some evidence for hydrocephaly. The radiograph was taken at one time so that size relations are absolute.

MOUSE SKELETON AT 4 MONTHS OF AGE FOLLOWING 100r X-RAYS TO EMBRYO



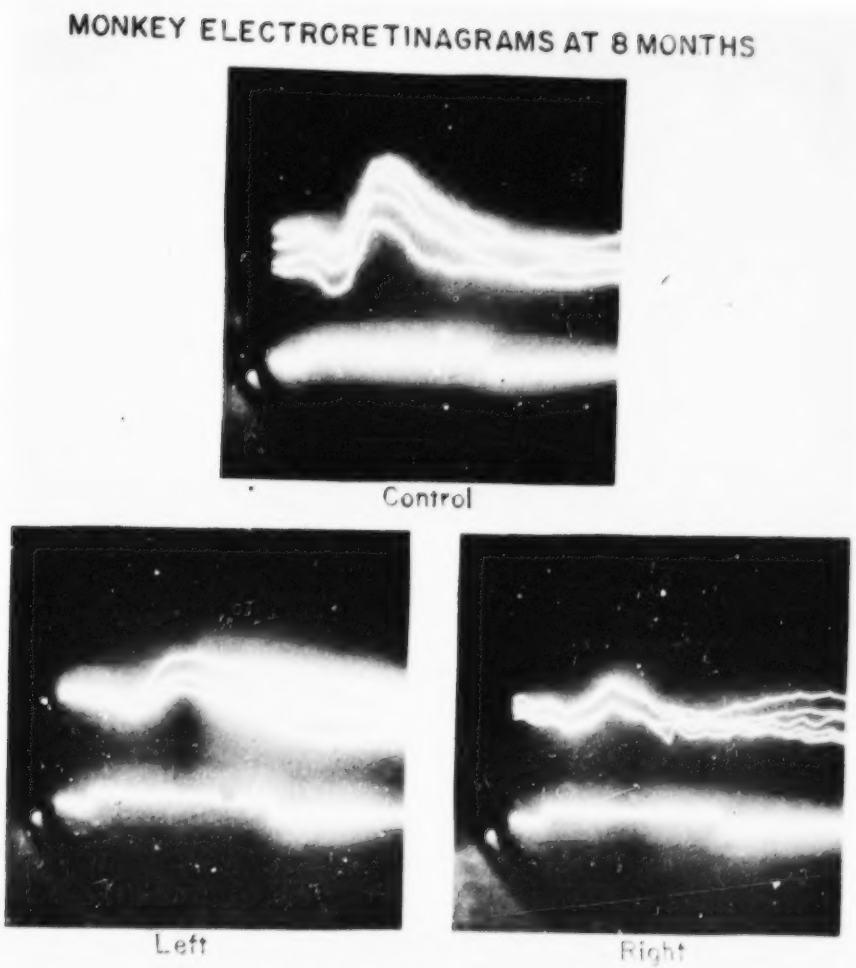


Fig. 19 Functional anomalies occur following irradiation of the mammalian fetus. These electro-retinograms of monkeys made when they were 23 months of age illustrate this. The upper is the control and the two lower photographs are records of the two eyes of a monkey exposed to 300 R x-rays at 60 days gestation (normal developmental period in the monkey is about 150 days). Note the depression in visual acuity which might not be evident from histological sections. (Rugh & Skaredoff 1969)

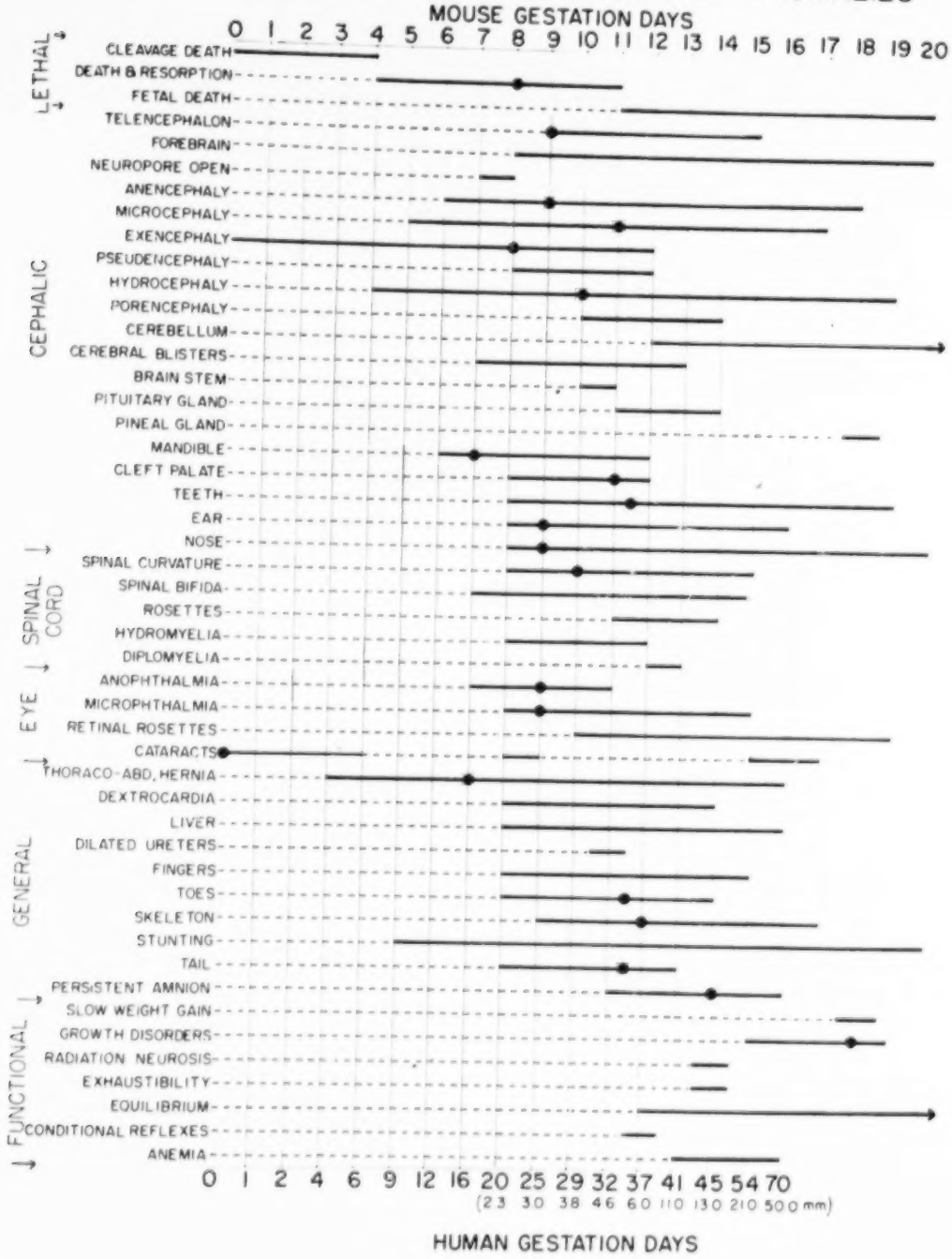
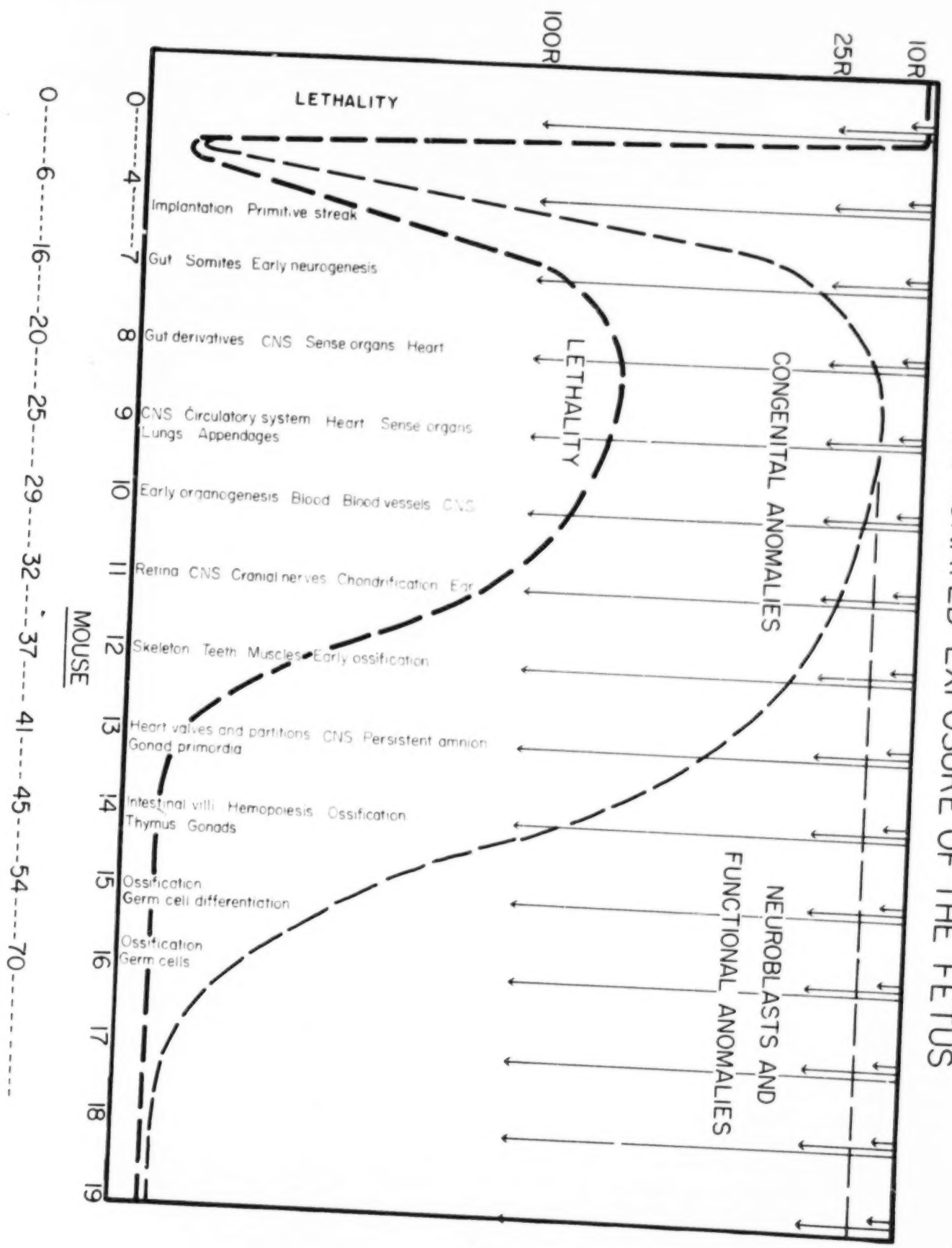


Fig. 20 This figure is a plot of the gestation days in mouse development when x-rays (ionizations) can be expected to cause certain congenital anomalies. Days are plotted in the vertical lines. The susceptible period for any anomaly is indicated by the solid line and the dot indicates the time of maximum incidence of the anomaly, following irradiation at that time. It will be noted that most of the anomalies are caused by irradiation at 8, 9, or 10 days which corresponds to 20-29 days for the human (below). When we extrapolate the developmental changes that occur in mouse and in man, it seems that the most radio-dangerous period for the human would be between the third and fourth week. However, since anomalies can be produced through day 14 in the mouse, it is suggested that the human fetus be protected against any unnecessary ionizing radiations at least until after the 6th week of development.

ORGAN DIFFERENTIATION AND RADIOSENSITIVITY


DAILY FRACTIONATED EXPOSURE OF THE FETUS
100R
25R
10R
LETHALITY
CONGENITAL ANOMALIES
NEUROBLASTS AND FUNCTIONAL ANOMALIES
Implantation Primitive streak
Gut Somites Early neurogenesis
Gut derivatives CNS Sense organs Heart
CNS Circulatory system Heart Sense organs Lungs Appendages
Early organogenesis Blood Blood vessels CNS
Retina CNS Cranial nerves Chondrification Ear
Skeleton Teeth Muscles Early ossification
Heart valves and partitions CNS Persistent amnion Gonad primordia
Intestinal villi Hemopoiesis Ossification Thymus Gonads
Ossification Germ cell differentiation
Ossification Germ cells
MOUSE
HUMAN
0 4 7 8 9 10 11 12 13 14 15 16 17 18 19
0 6 16 20 25 29 32 37 41 45 54 70

APPENDIX 2

BIBLIOGRAPHY DEALING WITH X-RADIATION AND THE HUMAN FETUS*

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